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Evaluation of optic disc microcirculation by optical coherence tomography angiography in patients with primary open angle glaucoma

Ocena unaczynienia tarczy nerwu wzrokowego u chorych na jaskrę pierwotną otwartego kąta za pomocą angiografii optycznej koherentnej tomografii

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Abstract:

Aim: To assess the vascular network length and area using optical coherence tomography angiography in patients with primary open angle glaucoma and healthy subjects.

Material and methods: The study group included 31 eyes of 21 patients with primary open angle glaucoma: 13 men (42%) and 18 women (58%), at the age of 31–86 years (mean age of 66 ± 12 years). The control group included 34 eyes of 21 healthy volunteers: 4 men (12%) and 30 women (88%), at the age of 35–70 years (mean age of 52 ± 9 years). All patients were examined using optical coherence tomography angiography.

Results: Within the superficial vascular layer, the mean vessel area was 30633 pixels and 3057 pixels in the study and control group, respectively ($p>.05$), whereas the mean vessel length was 16321 pixels and 15425 pixels in the study and control group, respectively ($p>.05$). Within the medium layer, the mean vessel area was 20117 pixels and 24675 pixels in the study and control group, respectively ($p<.05$), whereas the mean vessel length was 8880 pixels and 11111 pixels in the study and control group, respectively ($p<.05$). Within the choriocapillaris layer, the mean vessel area was 33175 pixels and 35417 pixels in the study and control group, respectively ($p<.05$), whereas the mean vessel length was 18243 pixels and 18114 pixels in the study and control group, respectively ($p>.05$).

Conclusions: In glaucoma patients, vascular abnormalities of the optic disc microcirculation can be observed. There was no significant difference in the superficial optic disc vascular network area and length between the groups. The middle depth vessel area was significantly smaller and capillary network shorter in glaucoma patients. Within the deep layer, the vessel area was significantly smaller in glaucoma patients, however, there was no significant difference in the vessel length between the groups. Optical coherence tomography angiography may be a useful tool for non-invasive monitoring of glaucoma patients.

Key words: microcirculation, primary open angle glaucoma (POAG), spectral optical coherence tomography with angiography function (AngioVue SOCT), optical coherence tomography angiography (OCT angiography – OCTA).

Abstrakt:

Cel: ocena unaczynienia (łącznej powierzchni i długości naczyń krwionośnych) u chorych na jaskrę pierwotną otwartego kąta (JPOK), w odniesieniu do parametrów u zdrowych osób z grupy porównawczej.

Materiał i metody: do grupy 1. włączono 31 oczu 21 chorych na jaskrę pierwotną otwartego kąta –13 mężczyzn (42%) i 18 kobiet (58%) w wieku od 31 do 86 lat (średnio 66 ± 12 lat). Do grupy 2. włączono 34 oczu 21 zdrowych ochotników – 4 mężczyzn (12%) i 30 kobiet (88%) w wieku od 35 do 70 lat (średnio 52 ± 9 lat). Wszystkich pacjentów zbadano za pomocą angiografii optycznej koherentnej tomografii.

Wyniki: w powierzchownej warstwie naczyń tarczy nerwu wzrokowego powierzchnia naczyń wyniosła 30633 piksele u badanych z grupy 1. i 30576 pikseli u osób z grupy 2. ($p>0,05$), długość naczyń zaś odpowiednio: 16321 pikseli oraz 15425 pikseli ($p>0,05$). W średnio głębokiej warstwie naczyń powierzchnia naczyń wyniosła 20117 pikseli u badanych z grupy 1. i 24675 pikseli u osób z grupy 2. ($p<0,05$), długość naczyń zaś odpowiednio: 8880 pikseli oraz 11111 pikseli ($p<0,05$). W głębokiej warstwie naczyń powierzchnia naczyń wyniosła 33175 pikseli u badanych z grupy 1. i 35417 pikseli u osób z grupy 2. ($p<0,05$), długość naczyń zaś odpowiednio: 18243 piksele oraz 18114 pikseli ($p>0,05$).

Wnioski: u pacjentów chorych na jaskrę zaobserwowano zaburzenia mikrokrążenia tarczy nerwu wzrokowego. Nie stwierdzono różnic w średniej powierzchni naczyń i długości naczyń na powierzchni tarczy nerwu wzrokowego pomiędzy grupami. Zaobserwowano, że w średnio głębokiej warstwie naczyń u badanych z grupy 1. mniejsze były zarówno powierzchnia naczyń, jak i ich długość. W głębokich warstwach naczyń ich powierzchnia była mniejsza u badanych z grupy 1. Nie zaobserwowano, aby długość naczyń u badanych z obu grup była różna. Angiografia optycznej koherentnej tomografii jest techniką przydatną do badania chorych na jaskrę i może stać się pomocnym badaniem uzupełniającym.

Słowa kluczowe: mikrokrążenie, jaskra pierwotna otwartego kąta, spektralna optyczna koherentna tomografia z funkcją angiografii (AngioVue SOCT), angiografia optycznej koherentnej tomografii (angiografia OCT – OCTA).

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Introduction

Glaucoma is an umbrella term for a group of ocular diseases which cause damage to the optic nerve and may lead to irreversible blindness (1). A characteristic feature of glaucoma is the progressive optic nerve damage with the loss of retinal ganglion cells (2).

Previous studies have shown that apart from increased intraocular pressure, vascular factors may play an important role in the development of glaucoma (3). Understanding the relationship between the retinal vessel area and length, and glaucoma may improve our knowledge of the role of retinal blood flow in the pathophysiology of glaucoma.

The recently developed method of optical coherence tomography angiography (OCTA) enables a noninvasive assessment of blood vessels, both of the retina and the optic disc (4). OCTA enables a detailed visualization of the retina, the optic disc and the choroid. The technique is non-invasive and it does not require using any contrast medium. Decorrelation OCTA detects changes in the amplitude of flow-related reflection spectrum. Consecutive B-scans of a given cross-section are acquired and compared. A number of repeated B-scans creates a high-quality 3D image (4).

OCTA enables a simultaneous evaluation of the retinal structure and microcirculation. The advantages and disadvantages of the OCTA, as compared to the fluorescein angiography (FA), have been recently discussed (5, 6). The key advantage of OCTA is its high resolution (5). The acquired images have superior quality in visualising microvascular network, thus revealing even small abnormalities and vascular irregularities (7).

Purpose

The purpose of this study was to assess and compare the mean length and the mean area of the optic disc vascular network in eyes with primary open angle glaucoma (POAG) and in healthy eyes using spectral optical coherence tomography with angiography function (AngioVue SOCT).

Material and methods

The analysed data was gathered prospectively from a non-randomized consecutive series of patients as a part of an observational study. All patients gave an informed consent to participate in the study. All tenets of the Declaration of Helsinki were followed for all study protocols. The study was approved by the Bioethics Committee of the Medical University of Lodz (number RNN/283/17/KE).

The patients were divided into two groups. The study group consisted of 31 eyes (16 right and 15 left eyes) of 21 patients with known POAG. This group included 9 men (42.8%) and 12 women (57.2%), aged from 31 to 86 years (mean age of 66 $\pm$ 12 years). The mean duration of POAG was 12 $\pm$ 8 years. The control group consisted of 34 eyes (18 right and 16 left eyes) of 21 healthy volunteers without glaucoma or any other ocular disease. This group included 19 women (90.5%) and 2 men (9.5%), aged from 35 to 70 years (mean age of 52 $\pm$ 9 years). The exclusion criteria were: any previous ocular surgery, laser procedures or any present or previous ocular diseases (except for glaucoma in the study group).

All patients underwent the eye fundus examination including optical coherence tomography (OCT) examination using a high-speed 840-nm-wavelength spectral-domain optical coherence tomography instrument Optovue (Avanti RTVUE XR). Only the best quality scans were evaluated. The Optovue (Avanti RTVUE XR) device used in our study can acquire "en face" 3.0 x 3.0 mm or 4.5 x 4.5 mm scans. Angioflow scans show patent blood vessels on a selected depth of the retina or the optic disc. The following levels of blood vessels can be visualized: 1. superficial retinal or optic disc vessels, showing the central retinal artery and its branches – "Nerve head" image; 2. vessels at the level of the vitreous body (i.e. neovascularization of the optic disc) – "Vitreous" image; 3. vessels present in the middle layers of the peripapillary nerve fibers – "Radial Peripapillary Capillaries" (RPC) image; 4. vessels at the level of the retinal pigment epithelium (RPE) and deep layers of the optic disc – "Choroid/Disc" image.

The assessed parameters included:

1. Retinal and optic disc capillaries

En-face OCT angiography images of the superficial capillary plexus, deep capillary plexus, outer retina and choriocapillaris area were used. Scans were performed at three depths: 1. the superficial vascular layer of the optic nerve disc, 2. the middle vascular layer at the level of the radial peripapillary capillaries, and 3. the deep vascular layer at the level of choriocapillaris. The total blood vessel area and total blood vessel length were measured.

In order to analyze the retinal capillary network angioflow scans were used. We used the same type of scans in all patients, showing black vessels on white background in a 3.0 x 3.0 mm square area – all images had 304 x 304 = 92416 pixels (px). As the software provided by the OCT manufacturer does not enable measuring the parameters of the capillary network, publicly available freeware graphical analysis software Image J was used, in line with the procedure described below. First, we wanted to evaluate the total area of capillaries visible in the peripapillary region. Therefore, the grayscale image (Fig. 1A) was converted to black and white only (Fig. 1B) and a histogram was generated (Process – Binary – Make binary – Analyze – Histogram). Then, the total of black pixels (Histogram – List),

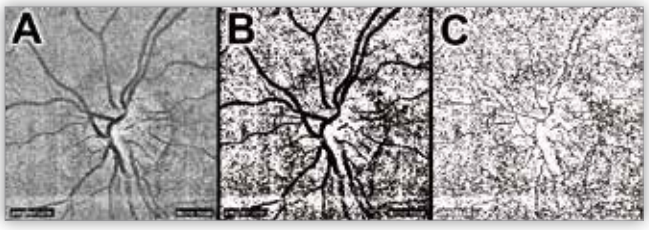

Fig. 1. Optic Disc scan acquired using OptoVue device, angioflow mode – A. Maximally contrasted scan. The number of black pixels corresponds to the total blood vessel area – B. Scan, where blood vessels were "skeletonized" i.e. reduced to 1 pixel width. The number of black pixels corresponds to the total length of the blood vessels – C.

Ryc. 1. Skany tarczy nerwu wzrokowego wykonane aparatem OptoVue w trybie „angioflow" – A. Skan maksymalnie skontrastowany. Liczba czarnych pikseli odpowiada całkowitej powierzchni naczyń krwionośnych – B. Skan, na którym dokonano redukcji grubości naczyń do jednego piksela. Liczba czarnych pikseli odpowiada całkowitej długości naczyń krwionośnych – C.

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which correspond to the total area of capillaries, was determined. Next, we wanted to calculate the combined length of visible capillaries whilst disregarding their width. In order to do so, the image had to be converted to single-pixel lines (Fig. 1C). A histogram was generated (Process – Binary – Make binary – Analyze – Histogram) and the total of black pixels (Histogram – List), which correspond to the total length of capillaries, was determined.

2. Cup to disc (C/D) ratio

The mean cup to disc (C/D) ratio was measured automatically by the OCT device. The data was read from the ONH Report (Optic Nerve Head) and the values obtained in both groups were compared.

Statistical analysis

All calculations were performed using Microsoft Excel and Addinsoft XLStat 2008 bundles. As the study sample was small, non-parametric tests were used for statistical analyses. The between-groups differences were determined using the two-tailed Mann-Whitney test for independent samples. The significance level $\alpha = .05$ was assumed for all comparisons.

Results

The OCTA device uses a motion-detecting algorithm, however, it does not offer a function to measure the area or the length of visualized blood vessels. Therefore, the data were extracted using Image J free software.

Optic nerve head superficial capillary network area

In maximally contrasted scans, the total of black pixels corresponds to the total superficial capillary network area of the optic nerve disc. The total of black pixels was 30633 px ± 2727 px and 30576 px ± 2422 px in the study and the control group, respectively. The difference was not statistically significant, $p>.05$. There was no difference in the total capillary network area in the optic disc between glaucoma patients and healthy subjects.

Optic nerve head superficial capillary network length

In scans with blood vessels reduced to 1 pixel width, the total of black pixels corresponds to the total superficial capillary network length of the optic nerve disc. The total of black pixels was 16321 px ± 1886 px and 15425 px ± 2339 px in the study and the control group, respectively. The difference was not statistically significant, $p>.05$. There was no difference in the total capillary network length in the optic disc between glaucoma patients and healthy subjects.

Radial peripapillary capillary network area

In maximally contrasted scans, the total of black pixels corresponds to the total radial peripapillary capillary network area. The total of black pixels was 20117 px ± 3349 px and 24675 px ± 2943 px in the study and the control group, respectively (Fig. 2). The difference was statistically significant, $p<.0001$. The total radial peripapillary capillary network area was significantly smaller in glaucoma patients as compared to healthy subjects.

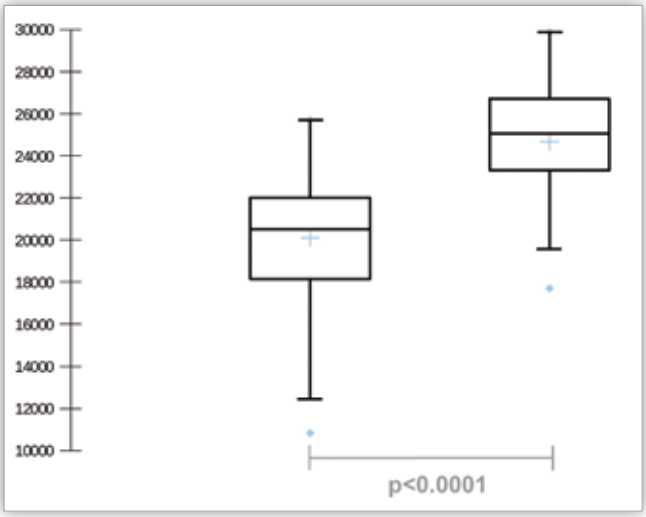

Fig. 2. Radial peripapilary capillary network area.
Ryc. 2. Powierzchnia sieci kapilar okołoplamkowych.

Radial peripapillary capillary network length

In scans with blood vessels reduced to 1 pixel width, the total of black pixels corresponds to the total radial peripapillary capillary network length. The total of black pixels was 8880 px ± 1702 px, and 11111 px ± 2259 px in the study and the control group, respectively (Fig. 3). The difference was statistically significant, $p<.0001$. The total radial peripapillary capillary network was significantly shorter in glaucoma patients as compared to healthy subjects.

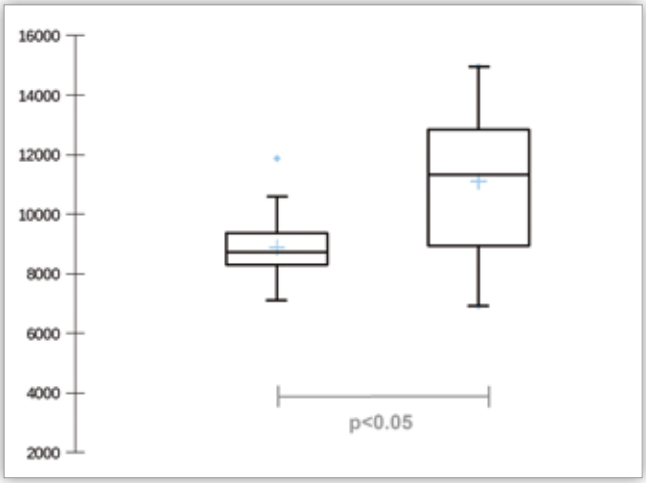

Fig. 3. Radial peripapillary capillary network length.
Ryc. 3. Długość sieci kapilar okołoplamkowych.

Choriocapillaris vascular network area

In maximally contrasted scans, the total of black pixels corresponds to the total choriocapillaris vascular network area. The total of black pixels was 33175 px 3915 px and 35417 px ± 3177 px in the study and the control group, respectively (Fig. 4). The difference was statistically significant, $p<.05$. The total choriocapillaris vascular network area was significantly smaller in glaucoma patients as compared to healthy subjects.

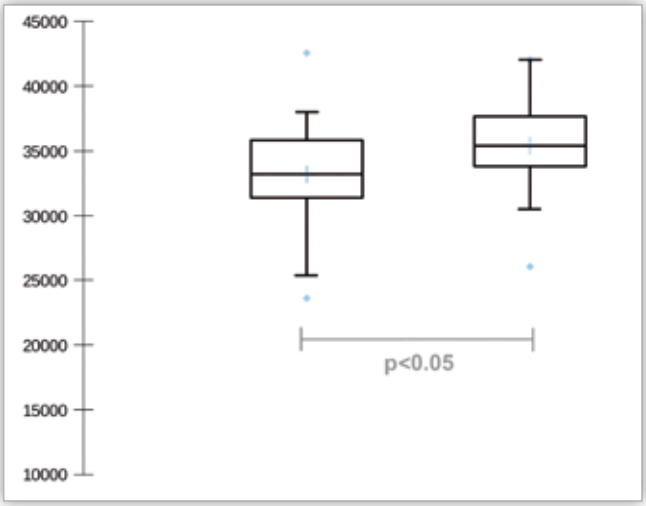

Fig. 4. Choriocapillaris vascular network area.
Ryc. 4. Powierzchnia sieci choriokapilar.

Choriocapillaris vascular network length

In scans with blood vessels reduced to 1 pixel width, the total of black pixels corresponds to the total choriocapillaris vascular network length. The total of black pixels was 18243 px ± 1826 px, and 18114 px ± 2691 px in the study and the control group, respectively. The difference was not statistically significant, $p>.05$. There was no difference in the total choriocapillaris vascular network length in the optic disc between glaucoma patients and healthy subjects.

Mean C/D ratio

The mean C/D ratio was 0.68 ± 0.12 and 0.32 ± 0.14 in the study and the control group, respectively. The difference was statistically significant ($p<.01$). The mean C/D ratio was significantly smaller in glaucoma patients as compared to healthy subjects.

Discussion

Microvascular changes of the optic nerve head have been previously found in patients with glaucoma (8). Recently, the angio-OCT technique has been evaluated by many authors also in patients with glaucoma (5–7). Some studies suggested that OCTA may be useful for early diagnosis and monitoring of glaucoma (9, 10). OCTA is a new method for the assessment of retinal microcirculation, optic disc and the choroid. Until now, fluorescein angiography has been the "gold standard" of imaging of the vascular network (11).

OCTA is based on high-resolution imaging of blood vessels. Its main advantage is being non-invasive, i.e. no dye injection is necessary. OCTA offers a better detail visualization than the FA, which enables the detection of early microvascular changes (7). Unlike FA, it provides images of both the superficial and deep retinal vascular plexuses which can be evaluated independently (12). The main limitations of angio-OCT are the same those of FA, i.e.: small size of scans, as well as the possibility to scan only the posterior pole. Furthermore, the assessment is only possible with clear optic media. OCTA can be performed through a non-dilated pupil, but mydriasis is helpful.

There are studies to support the utility of OCTA in microcirculatory evaluation in diabetic retinopathy, macular oedema of different origin, pre-, intra- and subretinal neovascularization, retinal vein occlusion, serous and hemorrhagic retinal detachment, various macular degenerations, optic disc disorders and glaucoma (6, 9, 12–14). Ours, however, is the first study to measure and analyse vascular network length and area in glaucoma using OCTA. These parameters can be derived from the OCTA scans using image processing and, in our opinion, they may become a valuable contribution for interpreting angio-OCT reports. The total vessel area and vascular network length can be used for quantifying the severity of vascular abnormalities. They were found to be significantly smaller in the middle vascular layers of the optic disc at the level of peripapillary capillaries in patients with POAG, in comparison with healthy subjects. Similarly, choriocapillaris vascular network area, but not length, was found to be significantly smaller in glaucoma patients.

Our results are in accordance with those presented to date by other authors. Akil et al. (15) evaluated the optic nerve vascular density using swept source OCTA in patients with early POAG, pre-perimetric glaucoma and normal eyes. The authors demonstrated a significant difference in vessel density between POAG eyes and controls. Furthermore, there was a significant difference in the peripapillary, optic nerve disc and papillary vessel density values between pre-perimetric glaucoma patients and controls. There was also a strong correlation between optic disc and papillary vessel density and the mean retinal nerve fiber layer (RNFL) thickness in eyes with POAG. Yarmohammadi et al. (16) compared the retinal nerve fiber layer thickness and OCTA retinal vessel measurements (i.e.: the vessel density map) in healthy subjects, glaucoma suspects and glaucoma patients, demonstrating significantly lower mean vessel density in glaucoma patients as compared to glaucoma suspects and healthy eyes. Chen et al. (17) evaluated the differences in perfusion of the optic nerve head between normal and glaucomatous eyes using OCTA. The authors examined 21 glaucoma patients and 20 healthy eyes and found significant differences in the optic disc perfusion between glaucomatous and healthy eyes. Furthermore, the values significantly correlated with disease severity and structural defects in glaucomatous eyes. Therefore, the authors concluded that OCTA-based assessment of optic disc perfusion may provide useful information for glaucoma detection and monitoring. Similarly, Leveque et al. (18) found that OCTA may detect reduced blood vessel density within the optic nerve head, which is associated with structural and functional damage in glaucoma.

The limitations of our study included a relatively small sample size and the fact that OCTA does not enable blood flow measurements. Nevertheless, we believe that our study may help improve our understanding of the POAG pathophysiology.

Conclusions

In glaucoma patients, vascular abnormalities of the optic disc microcirculation can be observed. OCTA is a useful non-invasive assessment method, which easily detects microvascular abnormalities, and may, therefore, be used for the evaluation of capillary network in glaucoma. It may become a valuable additional monitoring tool in glaucoma.

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